

Cerebral Embolic Protection Devices During Transcatheter Aortic Valve Implantation: Systematic Review and Meta-analysis

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Abstract

Background and Purpose: Silent ischemic embolic lesions are common following transcatheter aortic valve implantation (TAVI). The use of embolic protection devices (EPD) may reduce the occurrence of these embolic lesions. Thus, a quantitative overview and credibility assessment of the literature was necessary to draw more a robust message about EPD. Therefore, the aim of this meta-analysis was to study whether the use of EPD reduces silent ischemic and clinically evident cerebrovascular events associated with TAVI.

Methods: We conducted a comprehensive search to identify studies that evaluated patients undergoing TAVI with or without EPD. Random-effects meta-analyses were performed to estimate the effect of EPD compared with no-EPD during TAVI using aggregate data.

Results: Sixteen studies involving 1170 patients (865/305 with/without EPD) fulfilled the inclusion criteria. The EPD-delivery success rate was reported in all studies and was achieved in 94.5% of patients. Meta-analyses evaluating EPD versus without EPD strategies could not confirm or exclude any differences in terms of clinically evident stroke (RR: 0.70, 95%CI: 0.38-1.29; P=0.26) or 30-day mortality (RR: 0.58, 95%CI: 0.20-1.64; P=0.30). There were no significant differences in new-single, multiple or total number of lesions. The use of EPD was associated with a significantly smaller ischemic volume per-lesion (SMD: -0.52, 95%CI: -0.85, -0.20; P=0.002) and smaller total volume of lesions (SMD: -0.23, 95%CI: -0.42, -0.03; P=0.02). Subgroup analysis by type of valve showed an overall trend towards significant reduction in new-lesions per-patient using EPD (SMD: -0.41, 95%CI: -0.82, 0.00; P=0.05), driven by self-expanding devices.

Conclusion: The use of EPD during TAVI may be associated with smaller volume of silent ischemic lesions and smaller total volume of silent ischemic lesions. However, EPD may not reduce the number of new-single, multiple or total number of lesions. There was only very low

quality of evidence showing no significant differences between patients undergoing TAVI with or without EPD with respect to clinically evident stroke and mortality.

Keywords: aortic stenosis - TAVI - TAVR - stroke - embolic protection - GRADE

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) procedures have been associated with silent-ischemic cerebral embolism as assessed by diffusion-weighted magnetic resonance imaging (DW-MRI) or high-intensity transient signals (HITS) as assessed by transcranial Doppler.¹⁻⁶ Embolic protection devices (EPD) might reduce the risk of cerebral embolic ischemic lesions, either clinically-evident cerebrovascular accidents or silent ischemic lesions in patients undergoing TAVI. Nonetheless, the efficacy of EPD in the TAVI setting has only been investigated in studies with relatively small sample sizes that are underpowered for the endpoints studied and thus, subject to selection biases. Hence, a comprehensive systematic review with a rigorous methodology for quality and credibility assessment is required to better inform decision-making.

We therefore conducted a systematic review and meta-analysis to assess silent-ischemic lesions and clinically-evident cerebrovascular outcomes associated with TAVI procedures performed with and without EPD.

MATERIAL AND METHODS

Eligibility criteria

We included studies that evaluated patients who underwent TAVI with and without EPD. Studies included in the meta-analysis had to be parallel-group in design with one group having TAVI with EPD and the other having TAVI without EPD. To increase power of the feasibility analysis, we also included single-arm studies that evaluated the feasibility of performing TAVI with EPD. We included studies that evaluated one or more of the following outcomes within the 30-day after TAVI: EPD-delivery success, stroke or transient ischemic attack (TIA), death, new-silent ischemic lesions as assessed by DW-MRI or HITS, neurocognitive function as assessed by Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), center for

epidemiologic studies-depression (CES-D) scale or National Institutes of Health Stroke Scale (NIHSS). Endpoints, when available, were reported in accordance to Valve Academic Research Consortium-2.⁷ Reporting of outcomes had to include either crude events in each group or any risk/odds estimate (relative-risk [RR], hazard-ratio, odds-ratio) with 95% confidence intervals (CI).

Search strategy

We conducted a search of EMBASE, MEDLINE, CINAHL, Web of Science Core Collection, Cochrane Library, and conference abstracts, from conception to August 15th, 2016 using OvidSP (Ovid Technologies). **An additional study published after the systematic search was included due to its scientific relevance.** The exact search terms used were: (“transcatheter aortic valve implantation” OR “TAVI” OR “transcatheter aortic valve replacement” OR “TAVR”) AND “embolic protection device”. There was no restriction based on language of study and both abstracts and unpublished studies presented in conferences were included. A flow diagram is shown in Figure I-Supplement, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).⁸ Institutional review board approval and patient consent were not required because of the nature of this study as a systematic review and meta-analysis.

Study selection

Two reviewers (RB and KS) independently and in duplicate checked all titles and abstracts for studies that met the inclusion criteria. The full reports of potentially relevant studies were retrieved, and data was independently extracted. Cohen’s kappa coefficient was calculated to evaluate agreement between the two reviewers at the screening levels. Any discrepancies between reviewers were resolved by discussion after consulting with a third investigator (MAM).

Quality assessment

Risk of bias in the eligible studies was assessed separately for randomized studies, using A Cochrane Collaboration Risk of Bias Tool (ACROBAT),⁹ and Non-Randomized Studies of Intervention using the ACROBAT-NRSI.¹⁰ The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system¹¹ was used to determine the strength of evidence as high, moderate, low, or very-low based on risk of bias, consistency, precision, directness, and publication bias.

Data analyses

We used RevMan (Review Manager version 5.1.7, Nordic Cochrane Centre) to perform random-effects meta-analysis using the Mantel-Haenszel method to determine pooled RR of EPD compared with non-EPD, with regards to post-TAVI outcomes, for dichotomous data. Standardized mean difference (SMD) was used to combine EPD/non-EPD differences in continuous outcomes across studies and to standardize the results to a uniform scale. Due to insufficient pre/post-procedural data, we excluded case series from quantitative synthesis and assessed them qualitatively. Intention-to-treat analysis was followed whenever possible. When only median and interquartile-range were available, we estimated mean and standard deviation using formulas proposed by Wan and colleagues.¹² When only 95%CI was available, normal distribution was assumed when sample size was ≥ 100 and we calculated standard deviation using the equation proposed by Cochrane Handbook.¹³ The I^2 statistic was used to assess the heterogeneity across studies, with an $I^2 < 25\%$ considered low, $I^2 25-50\%$ moderate, and $I^2 > 75\%$ high heterogeneity. Cohen kappa agreement scores between the two reviewers with respect to title/abstract and full-text screening were 0.78 and 0.70, respectively, indicating moderate agreement. Subgroup analyses were performed to determine whether the study design or type of bioprosthesis influenced the treatment effect. Two-sided P-values of 0.05 were considered statistically significant.

RESULTS

Study population

A total of 16 studies¹⁴⁻²⁹ including 1170 patients (865/305 with/without EPD) fulfilled the inclusion criteria for the qualitative synthesis (Figure I-Supplement). The mean age was 81.7 years and 50.2% were female in 14 studies that reported both age and gender.^{14-23,26-29} The presence of baseline atrial fibrillation was reported in 9 studies,^{17-19,21,22,26,27,29} with a prevalence of 31.6% (285/902 patients). Previous stroke was reported in 14 studies,^{14-23,26-29} with a prevalence of 10.8% (111/1028 patients). More details can be appreciated in the Supplemental Results, Table I and Table II).

Risk of bias and quality of evidence

A complete description can be appreciated in the supplemental material and Table III-Supplement. The quality of overall evidence was low-to-very-low with the main limitation being serious risk of bias and imprecision. The GRADE summary of certainty in outcomes is presented in Table IV-Supplement.

30-day outcomes

Device type, access site, procedure-related outcomes and follow-up assessment for all included studies reporting crude rate of events are summarized in Table V-Supplement. The EPD-delivery success rate was reported in all studies¹⁴⁻²⁹ and was achieved in 94.5% (804/851) of patients, ranging 64% to 100%. All-cause mortality was reported in 9 studies^{17-22,27-29} and occurred in 3.0% (27/907) of patients; 9 studies with EPD^{17-22,27-29} with a 2.4% (15/626) rate and 6 studies without EPD^{17,18,22,27-29} with a 2.8% (8/281) rate. The incidence of stroke was reported in 15 studies^{14-23,25-29} and occurred in 4.3% (23/1139) of patients; including 3.7% (31/843) in 15 studies with EPD^{14-23,25-29} and 6.1% (18/296) in 7 studies without EPD.^{17,18,22,23,27-29} Meta-analysis evaluating EPD versus without EPD strategies could not confirm or exclude a difference

in clinically-evident stroke (RR: 0.70, 95%CI: 0.38-1.29; P=0.26) or 30-day mortality (RR: 0.58, 95%CI: 0.20-1.64; P=0.30), Figure II-Supplement.

Association of EPD versus No-EPD with silent ischemic lesions: DW-MRI assessment

The incidence of new-lesions was reported in 8 studies^{17,18,20,22,23,26-28} and occurred in 88.7% (305/344) of patients; 8 studies^{17,18,20,22,23,26-28} used EPD and reported a 86.9% (173/199) rate, and 6 studies without EPD^{17,18,22,23,28} reporting a 91% (132/145) rate. Multiple lesions were reported in 4 studies^{17,18,23,26} and occurred in 75.9% (101/133) of patients; 4 studies using EPD^{17,18,23,26} reported a rate of 78.4% (58/74 patients), and in 3 studies without EPD^{17,18,23} a rate of 72.8% (43/59 patients) was reported. The total number of new-lesions per-patient was reported in 6 studies,^{17,18,23,28-30} and ranged from 2.2 to 8.3 lesions per-patient with EPD, and 3.1 to 16.7 lesions per-patient without EPD. The total volume of lesions per-patient was reported in 6 studies,^{17,18,23,27-29} and ranged from an average of 88 to 466 mm³ per-patient with EPD, and 168 to 800 mm³ per-patient without EPD (Table 1).

Meta-analyses evaluating EPD versus without EPD strategies showed no significant differences in terms of patients with single lesions (RR: 0.70, 95%CI: 0.25-1.96; P=0.50), and total number of patients with new-ischemic lesions (RR: 0.98, 95%CI: 0.89-1.07; P=0.60) Figure III-Supplement. There was no difference in the incidence of multiple ischemic lesions with EPD use (RR: 1.14, 95%CI: 0.98-1.33; P=0.10), and number of lesions per-patient (SMD: -0.19, 95%CI: -0.71, 0.34; P=0.49) although the latter with high-degree ($I^2=82\%$) of heterogeneity, Figure 1. Those who underwent TAVI with EPD had lesions with smaller volume (SMD: -0.52, 95%CI: -0.85, -0.20; P=0.002) and consequently, a smaller total volume of ischemic lesions (SMD: -0.23, 95%CI: -0.42, -0.03; P=0.02), Figure 1.

Study design and type of valve subgroup analyses

In the subgroup analyses by study design, randomized trials, as compared with non-randomized studies, the use of EPD did not significantly reduce the incidence of stroke (RR: 0.70, 95%CI: 0.38-1.29; P=0.26) nor 30-day mortality (RR: 0.58, 95%CI: 0.20-1.64; P=0.30), Figure 2-A-B. Randomized studies showed significantly fewer number of lesions per-patient using EPD (SMD: -0.53, 95%CI: -1.02, -0.04; P=0.03), whereas in non-randomized studies, the use of EPD was associated to more silent lesions per patient (SMD: 0.69, 95%CI: 0.18-1.19; P=0.008). Overall difference did not show statistically significant effect (SMD: -0.19, 95%CI: -0.71, 0.34; P=0.49), however, with significant interaction ($I^2=91.3\%$, P=0.0007). Randomized studies showed a significantly smaller total volume of lesions per-patient with EPD (SMD: -0.22, 95%CI: -0.43, -0.01; P=0.04), whereas in non-randomized studies, there was no difference between EPD versus without EPD strategies (SMD: -0.26, 95%CI: -0.76, 0.23; P=0.29). Overall difference showed statistically significant effect (SMD: -0.23, 95%CI: -0.42, -0.03; P=0.02), Figure 2-C-D.

Subgroup analysis according to the type of valve (Figure 3) showed no statistical difference in terms of patients with new-lesions (RR: 0.96, 95%CI: 0.86-1.07; P=0.49). There was an overall trend towards significant reduction in number of lesions per-patient using EPD (SMD: -0.41, 95%CI: -0.82, 0.00; P=0.05), driven by the self-expanding device (interaction P=0.01, $I^2=85.1\%$). The use of EPD reduced the volume per lesion (SMD: -0.56, 95%CI: -0.94, -0.17; P=0.005), and showed a trend-towards reduction in total volume of lesions per-patient (SMD: -0.24, 95%CI: -0.49, 0.01; P=0.06). Based on the SENTINEL trial²⁹ that provided data on balloon-expandable Edwards SAPIEN-XT and SAPIEN-3 valves, separately, the EPD-arm showed no apparent benefit in terms of number of lesions and total volume of lesions when the SAPIEN-3 only (excluding SAPIEN-XT) was computed into the meta-analyses (Figure IV-supplement).

Impact of EPD versus No-EPD on neurocognitive function

The assessment of neurocognitive function for all included studies is detailed in Table 2. In comparative studies, patients were assessed by the MoCA before and after TAVI in 3 studies,^{17,22,27} and the proportion of patients with EPD showing worsening neurocognitive function ranged from 10.7 to 27.3%, and from 22.7 to 33.3% in patients without EPD. Three studies^{22,27,28} used the NIHSS and the proportion of patients with EPD worsening neurocognitive function ranged from 0% to 17.9% and 4.5 to 22.5 % in patients without EPD. The MMSE was used in one study¹⁷ and did not show differences between EPD versus without EPD strategies.

DISCUSSION

Imaging studies reported that silent ischemic embolic lesions commonly occurred in patients undergoing TAVI despite the fact of using EPD. Our meta-analysis suggests that the use of EPD may be associated with smaller volume of ischemic lesions. Yet, EPD may not necessarily lead to reductions in the number of new-single, multiple and total number of lesions and may be associated with a numerically increased risk of HITS in certain studies. No significant differences were found between patients undergoing TAVI either with or without EPD with respect to hard end-points such as clinically-evident stroke or mortality. Failure to deliver the EPD occurred in approximately 5% of patients.

Silent and clinically-evident ischemic cerebrovascular insults following aortic valve procedures

Previous studies have shown an incidence of new-silent cerebral ischemic embolic lesions following TAVI in up to 84%, whereas new persistent clinical neurological impairment was about 3-6%.¹⁻⁵ Silent lesions affected the two cerebral hemispheres and circulation territories in most of the patients.¹⁻⁵ Importantly, when DW-MRI was performed at follow-up, investigators

agreed with the fact that ischemic lesions tended to disappear shortly after the TAVI procedure.^{1,2,17,28}

Notably, looking at SAVR populations, new cerebral ischemic lesions were reported in up to 60% of patients;^{1,31-35} lesions were often multiple, mostly clinically silent and were found to be of a smaller volume when compared to TAVI.¹ Massé and colleagues³⁵ detected silent cerebral infarctions in 61% of the patients undergoing SAVR, however, the authors reported the highest (17%) rate of stroke so far. This study highlights the importance of performing a systemic and specialized neurological assessment following cardiac interventions.³⁵ Hereof, when routine neurological and DW-MRI assessment was performed in a TAVI population, clinically apparent neurologic deficits were matched with positive DW-MRI ischemic lesions in about 15% of controls in the DEFLECT-III trial.²²

It is worth to be mentioned that the available data from observational studies used 1.5-T MRI scanners. In this regard, the three randomized EPD studies, the MISTRAL-C,²⁷ CLEAN-TAVI²⁸ and SENTINEL²⁹ used 3-T MRI-scanners, although 11 patients in the CLEAN-TAVI underwent MRI in a 1.5-T scanner because of pacemaker-dependency.²⁸ Hence, one may think that tiny emboli might have been missed with a 1.5-T MRI scanner; on the other hand, the use of a 3-T MRI-scanner, which has a higher sensitivity, may have overestimate the lesions. Therefore, the interpretation of the current results might be difficult to correlate with the daily-basis clinical practice.

Type of TAVI device and its impact on silent ischemic embolism

The number and volume of ischemic lesions tended to be greater with the self-expanding device.^{22,27-29} Lansky et al.²² showed that the freedom from ischemic lesions, as assessed by DW-MRI, among patients undergoing TAVI with EPD using the balloon-expandable valve was about 30%, whereas all patients undergoing TAVI with the self-expanding CoreValve had ischemic

lesions despite the fact of using the TriGuard HDH (Keystone Heart, Caesarea, Israel) embolic deflection device that indeed, covers all brain territories. Moreover, these subjects accounted for the largest lesion-volumes in the EPD-group.²² This finding is in line with those of the CLEAN-TAVI²⁸ trial showing that almost 100% of patients exhibited new-ischemic lesions in the EPD-arm. The SENTINEL trial²⁹ further supports that self-expanding devices were associated with larger lesion volume as compared to the balloon-expandable Edwards SAPIEN-XT and SAPIEN-3 bioprostheses, and this is taking into consideration that the trial mainly used the new-generation self-expanding Medtronic Evolut-R device.²⁹ Furthermore, the sub-group of patients receiving the new-generation balloon-expandable SAPIEN-3 device appeared to obtain a less protective effect from the EPD (Figure IV-supplement).

Silent ischemic lesions and neurocognitive function after TAVI

There is a clear discrepancy between the incidence of new-ischemic lesions following TAVI and the rates of clinically-apparent neurologic impairment. Previous studies showed that the occurrence of silent-ischemic embolism was not associated with a measurable pre/post-TAVI impairment in neurocognitive function.^{1,2,4,5} Ghanem et al.² showed that the presence of transient clinical symptoms did not correlate with ischemic lesions revealed by DW-MRI. Moreover, Fairbairn and colleagues⁵ did not find association between the number of cerebral infarcts and the reported mental-health and quality-of-life assessments.⁵ Furthermore, two studies showed a significant improvement in MMSE scores 3 months after TAVI.^{6,36}

The PROTAVI-C study¹⁷ showed no differences with and without EPD in pre/post-procedural neurological evaluation using the NIHSS scale, nor cognitive assessment with the MMSE. The cognitive status evaluated by the MoCA showed significant improvement at 30-day compared with baseline in the EPD arm, but no differences over time without EPD.¹⁷ In this regard, the DEFLECT-III trial²² showed that after adjusting for age, the mean MoCA score

improved from baseline to discharge and 30-day in the EPD group; however, in the control group, the mean score declined from baseline to discharge but rebounded to approximately baseline levels at 30 days. Therefore, no statistically significance was observed between groups of treatment at 30-day follow-up.²² The SENTINEL trial²⁹ used a comprehensive neurocognitive assessment tailored for TAVI patients and designed to evaluate seven domains of neurocognitive function, and, the use of EPD did not show any change in neurocognitive function.

In terms of long-term follow-up, Ghanem and colleagues³⁷ reported that 91% of patients presented preserved cognitive performance throughout the first 2 years after TAVI. Notably, the age of the patient but neither the absence of silent cerebral embolism, nor the use of EPD affected cognitive trajectory in this study.³⁷

Finally, one should bear in mind the present concern about silent ischemic lesions and its potential negative (or not) impact on neurocognitive function once TAVI will be extended to younger and less-sick patients exhibiting a longer life-expectancy. Thus, further investigations are needed to improve the identification of patients at high-risk for embolization such as those with extensive atherosclerosis/complex aortic atheroma, porcelain aorta, carotid disease or left atrial appendage thrombus.^{5,38-40}

Limitations

The main limitation of this research lies with the small number of studies, patients and events informing each outcome, and the high-rate of loss to follow-up in most of studies. Patient-level data was not available, precluding therefore a more robust adjustment for any differences in baseline data, such as atrial fibrillation, previous stroke, peripheral vascular disease, or anatomical variables. Also, due to insufficient data, we were not able to obtain summary mean estimates of pre/post-procedural values for neurocognitive endpoints. Nevertheless, in studies

where clinical, demographics and anatomical features were reported, populations were well-balanced in terms of baseline characteristics across the study groups.

CONCLUSION

Our analysis suggests that TAVI procedures with EPD might be associated with smaller volume of silent ischemic lesions. However, EPD might not reduce the number of new-single, multiple and total number of lesions. Moreover, there was only very-low quality of evidence showing no significant differences between patients undergoing TAVI with or without EPD with respect to clinically evident stroke and mortality. Further adequately-powered research studies are needed to ascertain differences in patient-important outcomes before EPD should be incorporated into routine TAVI practice.

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Table 1. Silent embolism

| Author, year | Type of EPD | Time-frame Imaging assessment | Outcomes | Patients with EPD | Patients without EPD |
|--|--------------------------------|--|---|--|--|
| Nietlispach et al. 2010 | Embrella Embollic Deflector | Pre-discharge DW-MRI | A 5-mm acute cortical infarct in the right temporal lobe in the patient that underwent balloon aortic valvuloplasty alone. | 0 (0) | N/A |
| Naber et al. 2012 | Claret CE Pro | N/A | N/A | N/A | N/A |
| Onsea et al. 2012 | Embrella Embolic Deflector | <7 days DW-MRI | Number of DW-MRI lesions per patient (compared to an historical control, n=20) | 3.2 | 7.2** |
| Rodés-Cabau et al. 2014 PROTAVI-C pilot study | Embrella Embolic Deflector | Periprocedural TCD Day ≤7 and 30 DW-MRI | HITS Patients with new lesions: day ≤7 Patients with single lesions Patients with multiple lesions Lesion volume, per lesion Lesion volume, per patient Patients with any post-TAVI lesions: day 30 | 632 (347-893) 34/34 (100) 4 (11.8) 30 (88.2) 30 (20-50) 43.0 (27.5–85.0) 0/26 (0)* | 279 (0-505) 6/6 (100) 1 (16.7) 5 (83.3) 50 (30-70)√ 47.5 (32.5–91.1) 0/5 (0.0) |
| Samim et al. 2015 | Embrella Embolic Deflector | Day 4 DW-MRI | New brain lesion Lesion number Lesion volume | 15/15 (100) 9 (4-12) 15.2 (11-22) | 35/37 (95) 5 (2-7)√ 25.1 (11-61) |
| Van Mieghem et al. 2015 | Montage Dual Filter | N/A | N/A | N/A | N/A |
| Baumbach et al. 2015 DEFLECT I | TriGuard | Periprocedural TCD Day 4 and 30 DW-MRI | HITS Patients with new lesions Number of new lesions Single lesion volume Total lesion volume | 836±134 23/28 (82) 3.0 (1.8-8.0) 30 (10-60) 200 (30-400) | - 76%# 2 (0.5-4.5)# 150# 300# |

| | | | | | |
|---|--|--|--|--|--|
| Schofer et al. 2015 | Claret Montage and Claret Sentinel | N/A | N/A | N/A | N/A |
| Lansky et al. 2015 DEFLECT III | TriGuard | Day 4 and 30 DW-MRI | Freedom from ischemic brain lesions (ITT): day 4 New brain lesions: day 30 Single lesion volume Maximum lesion volume | 7/33 (21.2) 3/26 (11.5) 30.9 58.5 | 3/26 (11.5) 2/22 (9.1) 34.8 68.3 |
| Wendt et al. 2015 | EMBOL-X Trans-aortic | Day 7 DW-MRI | New brain lesion Lesion volume | 8/14 (57.1) 88±60 | 11/16 (68.8) 168±217 |
| Van Gils et al. 2015 | Claret Sentinel plus Wirion | N/A | N/A | N/A | N/A |
| Schmidt et al. 2015 | Claret Cerebral Protection System | Day 3 | N/A | N/A | N/A |
| Samim et al. 2016 DEFLECT II Pilot Study | TriGuard HDH | Day 4 DW-MRI | Patients with new lesions Patients with single lesions Patients with multiple lesions Lesions per patient Mean lesion volume per patient | 10/11 (91) 2/11 (18) 8/11 (73) 5.5 (0-12.0) 13.8 (3.4-106.9) | 35/37 (95)** 4/37 (11)** 31/37 (84)** 5.0 (2.0-7.0) 25.1 (11.0-61.0)** |
| Van Mieghem et al. 2016 MISTRAL-C | Claret Sentinel | Periprocedural TCD Day 5 and 30 DW-MRI | HITS Single lesion volume Total lesion volume | 902±444 48 (10-60) 95 (10-257) | 695±259 75 (40-85) 197 (95-525)√ |
| Haussig et al. 2016 CLEAN-TAVI | Claret Montage | Periprocedural TCD Day 2, 7 and 30 DW-MRI | HITS New lesion (day 2) Total lesion number: day 2 Total lesion volume: day 2 Total lesion number: day 7 Total lesion volume: day 7 | 3196 (2522-4010) 48/49 (98) 8 (5.0-12.0) 466 (349-711†) 5 (2.75-8.0) 205 (115-338†) | 3674 (2551-5217) 44/45 (98) 16 (9.75-24.25)√ 800 (594-1407†)√ 10 (3.0-18.0) 472 (385-909†)√ |

| | | | | | |
|------------------------------------|-----------------|---------|--|--------------------------|---------------------------|
| Kapadia et al. 2017 SENTINEL | Claret Sentinel | Day 2-7 | Total lesion number: day 2-7 Total lesion volume: day 2-7 | 3 (2-10) 294 (69-786) | 5 (2-10) 310 (106-860) |
|------------------------------------|-----------------|---------|--|--------------------------|---------------------------|

Data presented as number/sample size (percentage), mean \pm SD or median (interquartile range or †95% confidence interval). DW-MRI: diffusion-weighted magnetic resonance imaging; TCD: transcranial Doppler; HITS: high-intensity transient signal. N/A: not available or applicable. ITT: intention-to-treat. *Two patients with stroke/TIA did not undergo repeat MRI due to pacemaker implantation. **Historical controls. #No contemporaneous comparator, the authors reported pooled data from several previous publications. Lesion volume expressed in mm³. √P=statistically significant.

Table 2. Neurocognitive function assessment

| Author, year | EPD | Assessment definitions | Outcomes | Patients with EPD | Patients without EPD |
|--|--------------------------------|-----------------------------------|---|---|--|
| Nietlispach et al. 2010 | Embrella Embolic Deflector | No neurocognitive assessment | N/A | N/A | N/A |
| Naber et al. 2012 | Claret CE Pro | NIHSS | Minor stroke (NIHSS score 2) Major stroke (NIHSS scores 4 and 9) | 1/40 (2.5) 2/40 (5.0) | N/A |
| Onsea et al. 2012 | Embrella Embolic Deflector | No neurocognitive assessment | N/A | N/A | N/A |
| Rodés-Cabau et al. 2014 PROTAVI-C pilot study | Embrella Embolic Deflector | NIHSS MMSE MoCA | MMSE: baseline MMSE: day 30 MoCA: baseline MoCA: day 30 | 28 (26-29) 28 (26-29) 24 (21-27) 25 (23-28)✓ | 27 (21-30) 28 (23-30) 24 (21-27) 26 (23-27) |
| Samim et al. 2015 | Embrella Embolic Deflector | No neurocognitive assessment | N/A | N/A | N/A |
| Van Mieghem et al. 2015 | Montage Dual Filter | No neurocognitive assessment | N/A | N/A | N/A |
| Baumbach et al. 2015 DEFLECT I | TriGuard | MoCA | MoCA: screening MoCA: discharge MoCA: follow-up | 23 (15-29) 24 (16-30) 25 (15-30)✓-fff | N/A |
| Schofer et al. 2015 | Claret Montage and Sentinel | No neurocognitive assessment | N/A | N/A | N/A |
| Lansky et al. 2015 DEFLECT III | TriGuard | NIHSS MoCA | NIHSS worsening: day 30 MoCA worsening: day 30 | 3.8% 27.3% | 4.5% 33.3% |
| Wendt et al. 2015 | EMBOL-X Trans-aortic | No neurocognitive assessment | N/A | N/A | N/A |

| | | | | | |
|---|--------------------------------------|--|---|---|---|
| Van Gils et al. 2015 | Claret Sentinel plus Wirion | No neurocognitive assessment | N/A | N/A | N/A |
| Schmidt et al. 2015 | Claret Cerebral Protection System | No neurocognitive assessment | N/A | N/A | N/A |
| Samim et al. 2016 DEFLECT II Pilot Study | TriGuard HDH | NIHSS | NIHSS worsening | 1/14 (7.1) | N/A |
| Van Mieghem et al. 2016 MISTRAL-C | Claret Sentinel | MoCA MMSE CES-D NIHSS | MMSE worsening MoCA worsening CES-D worsening NIHSS worsening | 4% 13% 8% 0% | 27% [√] 26% 25% 5% |
| Haussig et al. 2016 CLEAN-TAVI | Claret Montage | New neurological symptom assessed by a NIHSS- trained specialist | NIHSS worsening: day 2 NIHSS worsening: day 7 NIHSS worsening: day 30 | 17/44 (39) 11/44 (25) 7/39 (18) | 16/45 (36) 11/45 (24) 9/40 (23) |
| Kapadia et al. 2017 SENTINEL | Claret Sentinel | Neurocognitive function (attention, executive function, processing speed, verbal and visual memory, mental status, depression) | Δ overall composite score: day 2-7 Δ overall composite score: day 30 Δ overall composite score: day 90 | -0.33 \pm 0.65 -0.09 \pm 0.44 0.18 \pm 0.38 | -0.16 \pm 0.58 -0.03 \pm 0.37 0.18 \pm 0.35 |

Data presented as number/sample size (percentage), or median (interquartile range) or absolute percentage. N/A: not available or applicable. MMSE: Mini-Mental State Examination. MoCA: Montreal Cognitive Assessment. CES-D: Center for Epidemiologic Studies-Depression scale. NIHSS: National Institutes of Health Stroke Scale. ITT: intention-to-treat. PP: per-protocol analysis. N/A: not available. [√]P=statistically significant. ^{|||}: linear trend.

Figure legends

Figure 1. Meta-analyses evaluating silent ischemic embolic lesions for patients undergoing transcatheter aortic valve implantation with and without embolic protection device (EPD) as assessed by diffusion-weighted magnetic resonance imaging. M-H: Mantel-Haenszel. CI: confidence interval. Std: standardized mean difference. *Data extracted from author's oral presentation.³⁰

Figure 2. Meta-analyses evaluating (A) stroke and (B) mortality at 30-day (C) number of lesions, and (D) total volume of lesions, for patients undergoing transcatheter aortic valve implantation with and without embolic protection device (EPD), according to the study design. M-H: Mantel-Haenszel. CI: confidence interval. Std: standardized mean difference. *Data extracted from author's oral presentation.³⁰ †: EPD arm included both safety and device groups.

Figure 3. Meta-analyses evaluating silent ischemic embolic lesions for patients undergoing transcatheter aortic valve implantation with and without embolic protection device (EPD), according to the type of valve. M-H: Mantel-Haenszel. CI: confidence interval. Std: standardized mean difference. *Data extracted from author's oral presentation.³⁰